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|---|---|
| SWITZER, JULIET CAROLINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/950,022 | ROTHSCHILD ET AL. | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *1-9,17-44,47-54,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16,45,46 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of group II in the paper filed 3/17/03 is acknowledged. The traversal is on the ground(s) that no separate search is required to search the non-elected groups as all claims are related as product and process of use, and can be reviewed in a single search since all polymorphisms are in the PRKAG3 gene. This is not found persuasive because though all of the claims are drawn to methods and products which recite polymorphisms within the PRKAG3 gene, each of these polymorphisms and combinations of polymorphisms requires separate search and consideration to determine their patentability with regard to both the prior art and the other statues, such as 112 1st paragraph.

The requirement is still deemed proper and is therefore made FINAL.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The specification recites a number of nucleic acid sequences that are not properly identified with sequence identifiers (see for example, p. 39 of the specification, and throughout, and also at least figures 1, 2A, and 2B).

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, as appropriate, a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the

insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

***Specification***

2. The disclosure is objected to because of the following informalities:

The specification refers to Figure 1 on page 38, but the figure being referred to within the text of the specification does not seem to be the same figure 1 as is present in the drawings as page 38 refers to a figure that would represent the mapping of the QTL to chromosome 15, while figure 1 of the specification is a nucleotide sequence. Page 42 also refers to figure 1. Likewise, p. 45 refers to a "Figure 2," but does not appear to be referring to the Fig. 2 present in the instant application.

Appropriate correction is required.

***Information Disclosure Statement***

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 10-16, 45, 46, 54, 55, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite because the preamble recites that the method is for screening animals to determine those more likely to exhibit improved meat quality traits, but the method steps recite steps of assaying a biological sample for the presence of a genotype. The method itself does not set forth how the assaying for the presence of a genotype relates to the screening for animals more likely to exhibit improved meat quality traits, and thus, it is unclear if the method is intended to identify animals more likely to exhibit improved meat quality traits or simply to genotype animals. The claim does not set forth which of the recited genotypes for positions 199 and 200 is in fact associated with improved meat quality traits. Claims 11-16 are also indefinite for this reason as they depend from claim 10 but do not clarify this issue.

Claims 10-16, 45, 46, 54, 55, and 56 are further in definite over the recitation "improved meat quality traits" because whether or not a particular meat quality trait is an improvement is entirely a relative matter, and thus, it is unclear what traits are being predicted by the methods. First, the claim does not set forth what the standard of comparison is for the improvement. That is, the animals identified by the screen will have improved meat quality traits compared to which other animals. Also, it is unclear what standard for improvement in meat quality traits is being applied in the instant methods, as one person's idea of an "improved" meat quality trait may be different from another person's idea of an improved meat quality trait. Applicant is referred to the abstract provided by Lundstrom *et al.* (J. Dairy Science, Vol. 1, Suppl. 1, p. 255, abstract number 1052) who discusses meat quality traits and teaches that a phenotype that is considered

within the industry as a negative trait (the RN- phenotype) is preferred by Swedish consumers but disliked by French consumers. Thus, simply to recite a method for screening for "improved meat quality traits" is indefinite because it is unclear in whose view the improvement is to be judged, and thus, it is not clear what would constitute an improved meat quality.

Claims 10-16, 45, 46, 54, 55, and 56 are indefinite because the recitation "said animal" in the assaying steps of the claims does not have proper antecedent basis in the claims because the claims do not previously refer to an animal but to animals.

Claims 10-16 are indefinite over the recitation that the "genotype" to be determined is characterized by "a polymorphism" in claim 10. This is confusing because a genotype is generally accepted to be a recitation of particular alleles present at a polymorphic site in a nucleic acid, yet in claim 10 the genotype is characterized by the presence of the polymorphism itself, regardless of the allele present at the particular positions in the PRKAG3 gene. Furthermore, the claim recites position numbers 199 and 200, but fails to provide any context or identification for the sequence within which these positions are located. Thus, these positions are arbitrary. Amendment of the claim to recite, for example, "...determining the genotype of said animal by assaying for the presence of a polymorphism in the PRKAG3 gene of said animal, wherein said polymorphism is associated with meat quality traits and wherein said polymorphism results in said animal having a valine at position 199 and an arginine at position 200 of the encoded PRKAG3 polypeptide or an isoleucine at position 199 and an arginine at position 200 of the encoded PRKAG3 polypeptide, wherein the amino acids of the PRKAG3 polypeptide are numbered as in instant SEQ ID NO: 2..." would overcome the concerns with regard to the "genotype" issue and the identification of the location of the polymorphisms.

Claims 10-16 are indefinite over the recitation "or its equivalent" in claim 10 because neither the specification nor the claims set forth or explain what makes a position an equivalent position. That is, it is unclear how to determine or what constitutes the equivalent position. Claim 10 sets forth that the equivalent is determined by a BLAST comparison, but it is unclear what one is to look for within a BLAST comparison to determine the equivalent of the polymorphic position in other PRKAG3 polypeptides. Claim 11 is indefinite for reciting "or its equivalent" for the same reasons as claim 10.

Claim 11 is indefinite over the recitation of "at nucleotide position 595" because the claim fails to provide a reference sequence for which position 595 is relevant. Thus, it is unclear what version of the PRKAG3 gene one should look at to determine position 595. Use of a sequence identifier to set forth the position would overcome this rejection.

Claims 12-13 are indefinite because it is unclear how or why one would use a short interspersed element polymorphism test, which is designed to detect SINE elements, to detect a single nucleotide polymorphism as is being detected in claim 12.

Claim 13 is indefinite because it is unclear what is meant for a primer to be "selected from and based upon" and further because the designators "RP1F" and "PN52R2" are arbitrary identifiers and it is unclear what these designations mean. Use of sequence identifiers is recommended.

Claim 16 is indefinite because it is unclear what is meant for a primer to be "selected from and based upon" and further because the designators "RNF" and "RNR" are arbitrary identifiers and it is unclear what these designations mean. Use of sequence identifiers is recommended.

Claims 45 is indefinite over the recitation that the "genotype" to be determined is characterized particular amino acids. This is confusing first, because the genotype is being determined for a genetic sample, yet the claim recites assaying for the presence of amino acids. Further, the claim does not set forth an identification for what protein the amino acid positions are imbedded within, and thus the recitation of particular positions recited in the claim are completely arbitrary. Furthermore, the claims is indefinite because it fails to set forth in the method steps how the purpose of the claim as recited in the preamble is accomplished. That is, the claim fails to set forth how assaying for the presence of a genotype results in determining an animal more likely to have favorable meat quality traits.

Claims 46 is indefinite over the recitation that the "genotype" to be determined is characterized particular amino acids. This is confusing first, because the genotype is being determined for a genetic sample, yet the claim recites assaying for the presence of amino acids. Further, the claim does not set forth an identification for what protein the amino acid positions are imbedded within, and thus the recitation of particular positions recited in the claim are completely arbitrary. Furthermore, the claims is indefinite because it fails to set forth in the method steps how the purpose of the claim as recited in the preamble is accomplished. That is, the claim fails to set forth how assaying for the presence of a genotype results in determining an animal more likely to have favorable meat quality traits.

Claims 54 and 55 are indefinite because they fail to set forth in the method steps how the purpose of the claim as recited in the preamble is accomplished. That is, the claim fails to set forth how assaying for the presence of a genotype results in determining an animal more likely to

have favorable meat quality traits. Furthermore the term "the PRKAG3" in the last line of the claims lacks proper antecedent basis in the claims.

Claims 56 is indefinite over the recitation that the "genotype" to be determined is characterized particular amino acids. This is confusing first, because the genotype is being determined for a genetic sample, yet the claim recites assaying for the presence of amino acids. Further, the claim does not set forth an identification for what protein the amino acid positions are imbedded within, and thus the recitation of particular positions recited in the claim are completely arbitrary. Furthermore, the claims is indefinite because it fails to set forth in the method steps how the purpose of the claim as recited in the preamble is accomplished. That is, the claim fails to set forth how assaying for the presence of a genotype results in determining an animal more likely to have favorable meat quality traits.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10-16, 45, 46, 54, 55, and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for**...

Methods for screening pigs to determine those more likely to exhibit higher ham or loin pH, lower ham Minolta, or lower loin Minolta, comprising screening a nucleic acid sample for codons in the PRKAG3 gene that would result in the presence of an isoleucine at position 199

and an arginine at position 200 of the encoded polypeptide, wherein the presence of a genotype homozygous for isoleucine is indicative of a pig that would exhibit higher ham or loin pH and lower ham Minolta than a pig with a different genotype at the codons encoding positions 199 and 200, and the presence of a genotype heterozygous or homozygous for isoleucine is indicative of a pig that would exhibit lower loin Minolta than a pig that does not have a nucleic acid that encodes a polypeptide with an isoleucine at position 200 of the polypeptide encoded by porcine PRKAG3. Furthermore, the specification is enabling for methods for screening pigs to determine those more likely to exhibit higher ham or loin pH, lower ham Minolta, or lower loin Minolta which comprises screening a nucleic acid sample for codons in the PRKAG3 gene that would result in the presence haplotype 3 (30T-52G-1991) as disclosed herein, wherein the presence of haplotype 3 indicates those pigs more likely to exhibit higher ham or loin pH, lower ham Minolta, or lower loin Minolta than pigs that do not have haplotype 3

...**does not reasonably provide enablement for** methods which screen any possible animal for the same predispositions, or methods which look at genes other than the PRKAG3 gene or methods which utilize polymorphisms or haplotypes other than those specifically indicated as being supported by enabling disclosure or methods which predict an increased likelihood of any and all favorable meat quality trait. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Breadth of the Claims and Nature of the Invention**

The rejected claims are drawn to methods of screening animals to determine those more likely to exhibit "improved meat quality traits," and comprise the steps of obtaining biological samples from animals and assaying for the presence of particular genotypes associated with improved meat quality traits.

Claim 10 is limited to assaying the PRKAG3 gene for the presence of a polymorphism that results in a valine at position 199 and arginine at position 200 or assaying for the presence of a polymorphism that results isoleucine at position 199 and arginine at position 200, or "its equivalent" as determined by BLAST comparison of SEQ ID NO: 2. Claims 11-16 further describe the process steps. Thus, claims 10-16 encompass methods which predict the presence of any meat quality trait in any animal.

Claim 45 recites a method of screening animals which comprises assaying for the presence of a genotype that results in threonine at amino acid position 30, a glycine at amino acid 52, and an isoleucine at amino acid 199. Claim 45 encompasses methods which predict the presence of any meat quality trait in any animal, and any gene in fact that encodes a polypeptide of at least 199 amino acids.

Claim 46 is drawn to a method of screening animals to determine those more likely to have favorable meat quality traits which comprises assaying for the presence of a genotype characterized by isoleucine at position 199 and arginine at position 200. Claim 46 encompasses methods which predict the presence of any meat quality trait in any animal, and any gene in fact that encodes a polypeptide of at least 200 amino acids.

Claim 54 is drawn to a method for screening animals to determine those more likely to have favorable meat quality traits comprising assaying for the presence of a genotype characterized by a combination of at least two polymorphisms in the PRKAG3 gene. Claim 54 encompasses methods which predict the presence of any meat quality trait in any animal, utilizing any possible polymorphism within the PRKAG3 gene that is associated with meat quality traits.

Claim 55 is drawn to a method for screening animals to determine those more likely to have favorable meat quality traits comprising assaying for the presence of a genotype characterized by the a combination of at least two polymorphisms in the PRKAG3 gene. Claim 55 encompasses methods which predict the presence of any meat quality trait in any animal, utilizing any possible polymorphism within the PRKAG3 gene that is associated with meat quality traits. Claim 55 also recites methods of predicting increased value for litter size, but these methods are non-elected.

Claim 56 recites a method of screening animals which comprises assaying for the presence of a genotype that results in threonine at amino acid position 30, a glycine at amino acid 52, and an valine at amino acid 199. Claim 45 encompasses methods which predict the presence of any meat quality trait in any animal, and any gene in fact that encodes a polypeptide of at least 199 amino acids.

The nature of the invention is that it relies on analysis of biological samples for the detection of particular alleles at present at polymorphic sites. Based on the presence or absence of particular alleles, one can presumably make assumptions about the likelihood of the presence or absence of meat quality traits. The invention sets forth a screen for animals possessing

"improved" meat quality traits, but does not set forth in whose eyes the improvement is to be measured. Meat quality is largely a matter of relative opinion, with some individuals preferring meat with particular traits and others preferring different traits. Thus, the judgment of an "improved" meat quality is largely subjective. For example, Lundstrom *et al.* discusses meat quality traits and teaches that a phenotype that is considered within the industry as a negative trait (the RN- phenotype) is preferred by Swedish consumers but disliked by French consumers. The invention encompasses the prediction of meat quality traits in any animal for which this might be of interest, and since a wide variety of animals are raised for meat production (including, for example, pigs, sheep, cows, buffalo, chickens, turkeys, geese, game hens, frogs, fish of all kinds, sharks), the scope of these claims is quite broad with respect to animal type encompassed.

**Direction Provided and Working Examples**

The specification teaches that "favorable meat quality trait" means a significant improvement in one of many measurable meat quality traits above a given population (p. 6). The specification further provides that examples of such traits include, but are not limited to, loin Minolta lightness, loin Japanese color score, loin marbling, loin pH, ham minolta lightness, ham pHu and drip loss or purge (p. 6-7). Other quality traits include meat juiciness and tenderness in sensory tests, percentage of fat in the meat, and meat texture measures.

Applicants provide examples which teach the analysis of an intercross between Berkshire and Yorkshire (BxY) pig breeds yielding 525 $F_2$ offspring, some F3 offspring, and the analysis of blood samples from a large collection of five different commercial lines of pigs (p. 38). Applicants removed from their analysis any samples that had a Q at position 200 of the encoded

polypeptide, thus all samples examined in applicant's analysis had the R200 genotype (p. 39). Within the founders of the BxY family and some $F_3$ individuals, applicants identified three missense mutations, at positions 30, 52, and 199 of the PRKAG3 polypeptide (p. 42). Applicants teach a novel missense mutation with the porcine PRKAG3 gene which results in a G52S substitution in the encoded polypeptide (p. 42).

Applicants completed a $F_2$ association study and found that all three of the missense mutations had significant effects on average glycogen and lactate content and on glycolytic potential (p. 43). Applicants further teach that for pigs, the most significant effects were revealed for the I199V polymorphism for the traits analyzed, including glycogen and lactate content and glycolytic potential measures, and also in some of the meat quality traits associated with these measures (p. 43). For example, pigs that were homozygous for the codon encoding isoleucine at position 199 had significantly higher ham pH and loin pH (Table 4, page 59). However, pigs that were heterozygous for the codon encoding isoleucine at position 199 did not display significantly different pH than pigs homozygous for the codon encoding valine at position 199. This is true for ham Minolta L and ham Minolta b as well. Only for the loin Minolta measures did the presence of a single codon encoding isoleucine predict a significant difference between the groups. Applicants teach that for five lines of commercial pig breads, across all breeds, I199V is kept in the model for six tested meat quality traits, G52S for ham pH, loin pH, loin Minolta L, and ham Minolta b, and T30N was kept in the model for ham Minolta L, loin Minolta L and ham Minolta b (p. 43). The specification teaches that across and within line analyses showed haplotype 3 (30T-52G-199I) as having the highest effect which was significantly different from each other haplotypes for ham pH. The specification does not

disclose any other significant relationships between meat quality traits and haplotypes, thus, methods for determining improved meat quality by assaying for the presence of haplotype 2 (as in claim 56) are not enabled by the instant specification.

With regard to the application of the methods taught in the instant specification to animals other than pigs, the specification merely asserts that "it is expected that the different alleles disclosed herein will also correlate with variability in this gene in other economic or meat-producing animals such as bovine, sheep, chicken, etc." The specification is silent with respect to the nucleotide or amino acid sequence of the PRKAG3 gene or encoded polypeptide from other such species of meat producing animals, and the specification does not provide any evidence that the polymorphisms disclosed herein are present in other animal species or that even if the polymorphisms are present that they are also indicative of any particular meat quality traits.

**State of the Art, Level of skill in the Art, and Level of Unpredictability in the Art**

The prior art teaches the RN- phenotype in pigs, which is associated with high glycogen content in Hampshire pig skeletal muscles (for example, Milan *et al.* 2000, and references cited therein). This phenotype is considered technically to have large effects on meat quality and processing, pigs meat from having the phenotype has low ultimate pH, reduced water-holding capacity and a reduced yield of cooked ham, however the mutation is considered to have beneficial effects on meat content (ABSTRACT, Milan *et al.*). Milan *et al.* isolated the porcine PRKAG3 gene and a identified human version of the gene. Milan *et al.* screened the entire coding region of the porcine PRKAG3 gene for polymorphisms, and identified five PRKAG3 polymorphic sites within the positions of the PRKAG3 gene that code for codons 30, 53, 193, 194, 199, 200, and 372 of the porcine PRKAG3 polypeptide (Table 1). Milan *et al.* teach that

only the R200Q allele was exclusively associated with RN-, with the "Q" version being present in the RN- pigs. The "Q" allele was found only in RN- Hampshire pigs, and neither the "Q" allele nor the RN- phenotype were observed in other breeds of pigs (Milan *et al.* p. 1249). Milan *et al.* also teach that with the in the RN- pigs a "V" is present at position 199 and an "I" is present in all rn+ pigs.

The prior art does not provide the nucleotide or amino acid sequences of other meat species of pigs, nor does the prior art provide any additional polymorphisms within the porcine PRKAG3 gene that are associated with meat quality traits.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with particular phenotypes. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a physiological state or physical trait. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease

associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the PRKAG3 gene, and in some cases shown that they are reliable markers of some meat traits, it remains highly unpredictable that any of these polymorphisms exist in other species of animals, and even if they do exist, that they are indicative of any particular phenotypic trait. Vincek *et al.* (Mammalian Genome 5, 376-379 (1994)) demonstrate that polymorphisms that are present in the beta globin region in human were not able to be located in chimpanzee and gorilla. Thus, simply because a particular polymorphism is present in one species of animal, there is no evidence that it will be present in another animal.

The ability to apply the assays disclosed in the instant specification to a wide range of animals relies on an assumption of a structure/function correlation across different species of animals, however, no evidence of such a relationship has been provided in the specification. The application of the instantly disclosed assay to additional species of animals requires one to assume that these particular polymorphisms will be present at "equivalent positions" in other

animals, however, applicant has not disclosed the importance of these polymorphisms for the function of the PRKAG3 gene or encoded polypeptide, and so it is difficult if not impossible to determine the equivalent positions in the undisclosed PRKAG3 genes of other animals. Applicant has not provided any guidance as to how to determine which amino acid position in the other species of animals would be the "equivalent" positions to amino acids 199 and 200 of the porcine PRKAG3 encoded polypeptide. The specification and claim 10 refer to using BLAST to make such a determination, but fail to clearly define what in fact makes the position and "equivalent"—for example, are only positions that are 199 and 200 in the homologues of other animals the equivalent, regardless of surrounding amino acids? Is a certain percentage of homology or a run of common amino acids required to determine the equivalent? Is the equivalent position based on the three dimensional structure of the encoded polypeptide, such that the equivalent polymorphic position would have to be in a similar morphological position in the encoded polypeptide? No guidance is provided in the specification to further guide the practitioner to the "equivalent" positions, and such a determination is highly unpredictable.

The prior art does not provide the sequence of the PRKAG3 gene in other meat producing animal species, and neither does the instant specification. Due to this lack of critical information about the sequence of the PRKAG3 gene in other animal species, at the time the invention was made it was not possible to even predict what the equivalent positions of the polymorphisms disclosed herein would be in other animals. Further, it is not even clear that the PRKAG3 gene in other species of meat producing animals would have the same effects on meat quality as the PRKAG3 gene in pigs. Juppner (Bone Vol. 17, No. 2, Supplement, August 1995: 39S-42S) teaches that despite significant structural conservation, rat, opossum, and human

PTH/PTHrP receptor homologs display distinct functional characteristics (ABSTRACT and p. 39S-40S). Thus, even if homologues of PRKAG3 gene were identified and sequenced in other animals, and even if these displayed polymorphisms, it is highly unpredictable as to whether these putative polymorphisms would be indicative of any particular meat traits in the animals.

**Quantity of Experimentation**

An extensive, and prohibitive amount of experimentation would be required to practice this invention commensurate with the full scope of these claims. Applicants have disclosed that two generations of animals were bred and screened and a large collection of blood samples for five different lines commercial pigs were collected and screened in order to establish relationships between the instantly disclosed polymorphisms and meat quality traits. Because there is no reason to expect that the instantly disclosed polymorphisms would exist in species of animals other than pigs, or that other polymorphisms exist within the PRKAG3 gene that are indicative of meat quality traits, screening for additional polymorphisms in pigs or other animal species would require breeding and screening hundreds of thousands of animals. There is no evidence, however, of any frequency of significant polymorphisms in other meat producing animals, a genus which encompasses fowl, mammals, and indeed, even some reptiles. Further, as noted above, even in positive matches, the PRKAG3 polymorphism may not correlate with meat quality traits, since such a correlation is highly unpredictable.

Thus, in light of the broad nature of the claims, the lack of examples and guidance in the specification beyond the teachings of polymorphisms in pigs associated with particular traits, the high level of unpredictability in the prior art, and the high quantity of experimentation necessary to practice the claimed invention commensurate with its full scope, it is concluded that undue

experimentation would be necessary to practice the claimed invention commensurate with its full scope.

***Priority***

8. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 10-16, 45, 46, 54, 55, and 56 of this application. This application claims priority to three provisional applications. None of these provide adequate support under 112 1st paragraph for the claims to their full scope for at least the same reasons why the instant specification does not provide adequate support for the claims. Furthermore, none of the provisional applications provides support for the methods which examine particular haplotypes since these provisional applications do not provide analysis of the relationship between meat quality traits and any particular haplotypes. Thus, the filing date for the elected claims is considered to be the instant filing date, 9/10/01.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 10-16, 45, 46, 54, and 55 are rejected under 35 U.S.C. 102(a) or 102(b) as being anticipated by Milan *et al.* (Science, 19 May 2000, Vol. 288, pages 1248-1251). Milan *et al.*

teach a method for screening animals to determine those more likely to exhibit improved meat quality traits comprising:

obtaining a biological sample of material from said animal (p. 1249);

and

assaying for the presence of a genotype characterized by a polymorphism in the PRKAG3 gene characterized by an amino acid of valine at position 199 and an amino acid of arginine at position 200 (Table 1, alleles 2-4) OR an isoleucine at position 199 and an arginine at position 200 (Table 1, allele 5)

Specifically, Milan *et al.* teach that animals with their alleles 2-5 have higher meat quality (as indicated by their having the rn+ allele) than animals that have allele 1 as designated by them. Milan *et al.* determine nucleotide sequence of the PRKAG3 coding sequence by RT-PCR analysis, and thus they amplify the section of the PRKAG3 gene that contains the polymorphism, including the region that contains the BsaHI site. This rejection applies to claim 12 insofar as sequencing the gene can be considered one method of testing for short interspersed elements. This rejection applies to claims 13 and 16 insofar as it is unclear what primers are required to meet the limitations of the claims, but so far as Milan *et al.* do perform amplification prior to detection of the polymorphisms.

Furthermore, Milan *et al.* teach a method wherein they detect a threonine at amino acid position 30, a glycine at amino acid 52 and an isoleucine at amino acid position 199. Such a detection takes place in their allele 5 which is an allele from rn+ pigs. In all of the alleles detected by Milan *et al.*, a glycine was encoded at amino acid 52 (see Fig. 2), and thus the

detection of such a nucleic acid encoding the amino acids recited in claim 45 is inherent in the methods taught by Milan *et al.*

***Conclusion***

11. A method which detects a nucleic acid encoding a serine at position 52 of the amino acid sequence of the porcine PRKAG3 gene as depicted in instant SEQ ID NO: 2 has not previously been disclosed in the prior art.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet Einsmann Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet Einsmann Switzer
Examiner
Art Unit 1634

May 12, 2003